REMARKS

Reconsideration of the above-identified application, in view of the following remarks, is respectfully requested.

I. STATUS OF THE CLAIMS

Claims 64-88 were pending in the subject application. By this Amendment, Applicants have canceled claims 85-88 without prejudice or disclaimer, and have added new claims 89-96. Accordingly, upon entry of this Amendment, claims 64-84 and new claims 89-96 will be pending.

Claim 1 has been amended to correct a typographical error. The strucure recited therein has been corrected. The amendment to claim 1 is not a narrowing amendment. No new matter has been added. Support for this amendment may be found inter alia, in the specification, as originally filed, on page 54, lines 2-4, page 58, line 32, and page 59, lines 7-10.

Applicants maintain that the addition of new claims 89-96 raise no issue of new matter. Support for new claim 89 may be found inter alia in the specification, as originally-filed, on page 149, lines 1-10 and page 192, example 104. Support for new claims 90-95 may be found inter alia in the specification, as originally-filed, on page 64, line 23 through page 65, line 5 and page 54, line 1 through page 59, line 1. Support for new claim 96 may be found inter alia in the specification, as originally-filed, on page 25, lines 4-14 and page 63, line 29 through page 65, line 21.

Accordingly, Applicants maintain that this amendment is fully supported by the disclosure. Applicants therefore respectfully request that the Examiner enter this Amendment.

II. REJECTION UNDER 35 USC § 112, SECOND PARAGRAPH

On page 2 of the Office Action, the Examiner rejected claims 85-88 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

The Examiner alleged that claims 85-88 provide for the use of the compound of claim 64, but since the claims do not set forth any steps involved in the method/process, it is unclear what method/process the Applicants are intending to encompass.

In response, in an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, Applicants have canceled claims 85-88, thereby rendering this rejection moot. Accordingly, Applicants respectively request that the Examiner withdraw this ground of rejection.

Furthermore, Applicants have added new claims 90 to 95. Applicants respectfully note that claims 90 to 95 are directed to a method of treating a subject suffering from an eating disorder, depression or obesity, which comprises administering to the subject a therapeutically effective amount of the compound of either claim 64 or claim 89. Applicants respectfully maintain that new claims 90 to 95 set forth steps involved in a method and/or process, i.e., how the use of a compound is actually practiced.

In light of the remarks made hereinabove, Applicants maintain that new claims 90 to 95 are definite as required by 35 U.S.C. 112, second paragraph.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

III. REJECTION UNDER 35 USC § 112, FIRST PARAGRAPH

On page 3 of the Office Action, the Examiner rejected claims 87-88 under 35 U.S.C. § 112, first paragraph. The Examiner acknowledged that the specification was enabling for eating disorders. The Examiner alleged that claims 87-88 are not adequately enabled for the range of disorders generically recited therein.

In response, in an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, Applicants have canceled claims 87-88, thereby rendering this rejection moot. Accordingly, Applicants respectively request that the Examiner withdraw this ground of rejection.

Furthermore, Applicants have added new claims 90 to 95. Applicants respectfully note that new claims 90 and 91 are directed to a method of treating a subject suffering from an eating disorder, new claims 92 and 93 are directed to a method of treating a subject suffering from obesity and new claims 94 and 95 are directed to a method of treating a subject suffering from depression. On page 3 of the May 21, 2004 Office Action the Examiner acknowledged that the specification was enabling for eating disorders. Accordingly, claims 90 and 91 will not be further discussed.

Applicants maintain that the specification provides evidence and/or a nexus that the antagonism of neuropeptide receptor Y5 would be useful for treating depression and obesity. Furthermore, Applicants note that the specification includes screening data indicating that the claimed compounds are Y5 antagonistic.

In addition, Applicants maintain that compounds which decrease the activity of the human Y5 receptor have been shown to be useful for treating depression. Applicants note that International Application No. WO 03/051397 (Exhibit 1), entitled "Neuropeptide Y5 Receptor Antagonists for Treating Depression, Anxiety and Dementia", filed on December 13, 2002 and assigned to Merck & Co., Inc., discloses the use of a neuropeptide Y5 antagonist to treat and/or prevent depression and anxiety disorders. Specifically, WO 03/051397 discloses in Example 3 the administration of a Y5 antagonist to guinea-pig pups which were isolated from their mothers and littermates. The administration of the Y5 antagonist resulted in attenuation of separation-induced vocalizations by the guinea-pig pups.

Applicants respectfully maintain that compounds which decrease the activity of the human Y5 receptor have been shown to be useful for treating obesity. Notably, International Application Nos. WO 97/019682, WO 97/020822 and WO 97/020823 (Exhibits 2-4, repsectively) disclose aryl sulfonamides and sulfamides derived from arylalkylamines and

sulfonamides containing heterocyclic systems, which are all claimed as Y5 antagonists and known to reduce feeding. Furthermore, the Examiner cited Wieland, *et al.* (Expert Opin. Investig. Drugs 9(6): 1327-1346, 2002, PubMed Abstract provided), which describes the use of Y5 receptor antagonists to treat human obesity.

In light of the remarks made hereinabove, Applicants maintain that new claims 92 to 95 are adequately enabled under 35 U.S.C. § 112, first paragraph.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

IV. REJECTION UNDER 35 § USC 101

On page 6 of the Office Action, the Examiner rejected claims 85-88 under 35 U.S.C. 101. The Examiner alleged that the claimed recitation of a use, without setting forth any steps involved in the process results in a claim which is not a proper process claim under 35 U.S.C. 101. The Examiner directed the Applicants' attention to *Ex parte Kunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F.Supp. 131, 149 USPQ 475 (D.D.C. 1966).

In response, in an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, Applicants have canceled claims 85-88, thereby rendering this rejection moot. Accordingly, Applicants respectively request that the Examiner withdraw this ground of rejection.

Furthermore, Applicants have added new claims 90 to 95. Applicant srespectfully note that claims 90 to 95 are directed to a method of treating a subject suffering from an eating disorder, depression or obesity, which comprises administering to the subject a therapeutically effective amount of the compound of either claim 64 or claim 89.

Applicants respectfully maintain that new claims 90 to 95 are directed to proper process claims as required under 35 U.S.C. 101 and respectfully request that this rejection be withdrawn.

V. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

On page 7 of the Office Action, the Examiner rejected claims 64-84 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,124,331. The Examiner alleged that although the conflicting claims are not identical, they are not patentably distinct from each other because the same tricyclic thiazole compound, its compositions and process of making such a composition, is also embraced in U.S. Patent No. 6,124,331. The Examiner noted that when m=1 and v=1, the compounds claimed in the US patent includes the instant compounds and its compositions and the process of making a composition.

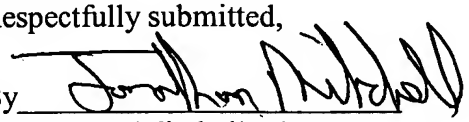
Applicants will consider filing a terminal disclaimer to overcome the obviousness-type double patenting rejection upon the indication of allowable subject matter.

In summary, in light of the remarks and amendments made hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection set forth in the May 21, 2004 Office Action and earnestly solicit allowance of the claims now pending in the subject application, namely claims 64 to 84 and claims 89 to 96.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned representative invites the Examiner to telephone him at the number provided.

Dated: August 20, 2004

Respectfully submitted,

By 

Jonathan P. Mitchell, Ph.D.
Registration No.: 50,239
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)
Attorneys/Agents For Applicant

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2003 (26.06.2003)

PCT

(10) International Publication Number
WO 03/051397 A1

(51) International Patent Classification[7]: A61K 45/00, 31/438, 31/352, A61P 25/22, 25/24, 25/28

(21) International Application Number: PCT/US02/40012

(22) International Filing Date:
13 December 2002 (13.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/341,542 17 December 2001 (17.12.2001) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MACNEIL, Douglas, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SHEARMAN, Lauren, P.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **VAN DER PLOEG, Leonardus, H., T.** [NL/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/051397 A1

(54) Title: NEUROPEPTIDE Y5 RECEPTOR ANTAGONISTS FOR TREATING DEPRESSION, ANXIETY AND DEMENTIA

(57) Abstract: This invention relates to the treatment and/or prevention of depression and/or anxiety disorders and/or dementia by the administration of a Neuropeptide Y Y5 antagonist. The present invention further provides for the use of a medicament for carrying out these methods.

side-effects include dry mouth, tachycardia, difficulty in visual accommodation, constipation, urinary retention, sexual dysfunction, cognitive impairment, postural hypotension, and weight gain.

Monoamine oxidase inhibitors are generally prescribed for patients who have failed to respond to tricyclic antidepressants or electroconvulsive therapy. As with tricyclic antidepressants, there are a number of side-effects associated with the use of MAOIs including dizziness, muscular twitching, insomnia, confusion, mania, tachycardia, postural hypotension, hypertension, dry mouth, blurred vision, impotence, peripheral edema, hepatocellular damage and leucopenia.

Of the new classes of antidepressant, selective serotonin reuptake inhibitors are increasingly prescribed, particularly in patients where the use of tricyclic antidepressants is contraindicated because of their anticholinergic and cardiotoxic effects. SSRIs such as fluoxetine, fluvoxamine, sertraline and paroxetine are generally non-sedating. Furthermore, SSRIs do not stimulate appetite and may therefore be appropriate in patients in whom weight gain would be undesirable. However, SSRIs are not without their own side-effects, including nausea, diarrhea, dry mouth, reduced appetite, dyspepsia, vomiting, headache, nervousness, insomnia, anxiety, tremor, dizziness, fatigue, decreased libido, pharyngitis, dyspnea, skin rash and sexual dysfunction.

Whatever drug is used, there is a delay of usually two, three or even four weeks before a therapeutic effect is observed. This period of delay may be particularly difficult for a patient suffering from a major depressive illness.

Anxiety is an emotional condition characterized by feelings such as apprehension and fear accompanied by physical symptoms such as tachycardia, increased respiration, sweating and tremor. It is a normal emotion but when it is severe and disabling it becomes pathological.

Anxiety disorders are generally treated using benzodiazepine sedative-antianxiety agents. Potent benzodiazepines are effective in panic disorder as well as in generalized anxiety disorder, however, the risks associated with the drug dependency may limit their long-term use, 5-HT_{1A} receptor partial agonists also have useful anxiolytic and other psychotropic activity, and less likelihood of sedation and dependence (See, e.g., R.J. Balderssarini in *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Edition, Chapter 18, McGraw-Hill, 1996, for a review).

fashion is an agonist wheras one that competitively reverses the NPY inhibition of forskolin-stimulated cAMP production is an antagonist.

Neuropeptide Y itself is the archetypal substrate for the NPY receptors and its binding can elicit a variety of pharmacological and biological effects *in vitro* and *in vivo*. When administered to the brain of live animals (intracerebroventricularly (icv) or into the amygdala), NPY produces anxiolytic effects in established animal models of anxiety such as the elevated plus-maze, Vogel punished drinking and Geller-Seifter's bar-pressing conflict paradigms (Heilig, M. et al. *Psychopharmacology* **1989**, *98*, 524; Heilig, M. et. al. *Reg. Peptides* **1992**, *41*, 61; Heilig M. et. al. *Neuropsycho-pharmacology* **1993**, *8*, 357). Thus compounds that mimic NPY are postulated to be useful for the treatment of anxiolytic disorders.

The immunoreactivity of neuropeptide Y is notably decreased in the cerebrospinal fluid of patients with major depression and those of suicide victims (Widdowson, P.S. et. al. *Journal of Neurochemistry* **1992**, *59*, 73), and rats treated with tricyclic antidepressants display significant increases of NPY relative to a control group (Heilig, M. et. al. *European Journal of Pharmacology* **1988**, *147*, 465). These findings suggest that an inadequate NPY response may play a role in some depressive illnesses, and that compounds that regulate the NPY-ergic system may be useful for the treatment of depression.

Neuropeptide Y improves memory and performance scores in animal models of learning (Flood, J. F. et. al. *Brain Research* **1987**, *421*, 280) and therefore may serve as a cognition enhancer for the treatment of neurodegenerative diseases such as Alzheimer's Disease (AD) as well as AIDS-related and senile dementia.

Elevated plasma levels of NPY are present in animals and humans experiencing episodes of high sympathetic nerve activity such as surgery, newborn delivery and hemorrhage (Morris, M. J. et. al. *Journal of Autonomic Nervous System* **1986**, *17*, 143). Thus chemical substances that alter the NPY-ergic system may be useful for alleviating migraine, pain and the condition of stress.

SUMMARY OF THE INVENTION

The present invention relates to the use of a NPY Y5 antagonist for treating depression in a mammal. Accordingly, the present invention provides a method for treating depression in a mammal comprising the administration of NPY Y5 antagonist. The present invention further provides a pharmaceutical composition

disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder.

Further exemplifying the invention is the use of a NPY Y5 antagonist for the treatment of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalized anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple etiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delirium, withdrawal delirium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid hemorrhage or cerebral edema.

hydroxy(lower)alkyl, hydroxy, lower alkoxy, halo(lower)alkoxy, lower alkylamino, di-lower alkylamino, lower alkanoyl and aryl;

n is an integer from 0 to1;

Q is selected from the group consisting of a single bond or carbonyl;

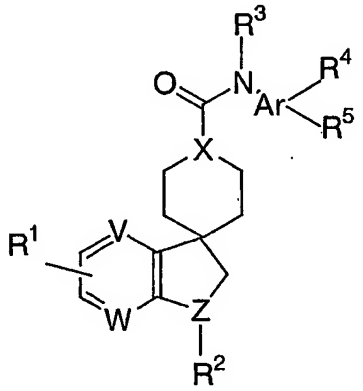
T, U, V and W are each independently selected from the group consisting of nitrogen or a methylene group, said nitrogen or methylene group may be optionally substituted with a substituent selected from the group consisting of: halogen, lower alkyl, hydroxy, and lower alkoxy;

X is selected from the group consisting of methylene or nitrogen;

Y is selected from the group consisting of nitrogen and oxygen, wherein said nitrogen may be optionally substituted with lower alkyl or oxygen;

and the pharmaceutically acceptable salts and esters thereof. These compounds are further described and methods of preparing them can be found in International Publication Number WO 01/14376, and in US Patent Nos. 6,326,375, and 6,335,345, which are hereby incorporated by reference in their entirety.

Non-limiting examples of NPY Y5 receptor antagonists include compounds of the formula:



or a pharmaceutically acceptable salt thereof, wherein;

- V, W, X and Z are independently selected from CH and N;

R^1 is H, C_{1-3} alkyl, C_{1-3} alkoxy, F, or Cl;

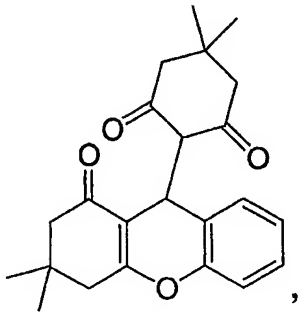
R^2 is $S(O)n\ R^6$, COR^6 or CHO, wherein

n is 0, 1 or 2; and

R^6 is $N(R^3)_2$ or C_{1-3} alkyl;

R^3 is independently H or C_{1-3} alkyl;

Non-limiting examples of NPY Y5 receptor antagonists include compound L-152,804 of the formula:



and pharmaceutically acceptable salts, esters and tautomers thereof. Compound L-152,804 and its preparation are disclosed in J. Organic Chemistry, vol. 31, No. 5, p. 1639 (1966); and U.S. Patent No. 6,258,837, which is hereby incorporated by reference in its entirety.

The above compounds are only illustrative of the NPY Y5 antagonists which are currently under investigation. As this listing of groups of compounds is not meant to be comprehensive, the methods of the present invention may employ any NPY Y5 antagonist and is not limited to any particular structural class of compound.

A suitable selection cascade for NPY Y5 antagonists of use according to the present invention is as follows:

(i) Determine affinity for human Y5 receptor in radioligand binding studies (Assay 1); select compounds with $IC_{50} \leq 10nM$, preferably $IC_{50} \leq 2nM$, especially $IC_{50} \leq 1nM$.

(ii) Determine ability of compounds to penetrate CNS by their ability to inhibit bovine pancreatic polypeptide (bPP)-induced food intake in Sprague-Dawley rats. Select compounds that inhibit (bPP)-induced food intake $ID_{50} \leq$ 30mg/kg p.o., and preferably $ID_{50} \leq 10$ mg/kg p.o. when administered 1 hour prior to central bPP agonist challenge.

Yet further preferred compounds of use in the present invention may be selected from those compounds which satisfy the NPY Y5 receptor binding criteria of step (i) which, in addition, have ≤ 5-fold shift in affinity when incubated in the presence of human serum albumin (HSA) to show non-specific protein binding.

Examples of NPY Y5 receptor antagonists of use in the present invention are the compounds described in US 6,191,160, US 6,313,298 and

the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

It will be appreciated that for the treatment of depression or anxiety, the NPY Y5 antagonist may be used in conjunction with other anti-depressant or anti-anxiety agents.

Suitable classes of anti-depressant agent include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical anti-depressants.

Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Another norepinephrine reuptake inhibitor of use in the present invention is reboxetine.

Suitable selective serotonin reuptake inhibitors include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

Suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof.

Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists include those compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677.

Suitable atypical anti-depressants include: bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof. Another suitable atypical antidepressant is sibutramine.

Other antidepressants of use in the present invention include adinazolam, alaproclate, amineptine, amitriptyline/chlordiazepoxide combination,

depressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of depression and/or anxiety.

For the treatment of the clinical conditions and diseases noted above, the compounds of this invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Preferably the compositions containing an the NPY Y5 antagonists of use according to the present invention are in unit dosage forms such as tablets, pills, capsules, wafers and the like. Additionally, the NPY Y5 antagonists of use according to the present invention may be presented as granules or powders for extemporaneous formulation as volume defined solutions or suspensions. Alternatively, the NPY Y5 antagonists of use according to the present invention may be presented in ready-prepared volume defined solutions or suspensions. Preferred forms are tablets and capsules.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such

The pharmaceutical composition is preferably provided in a solid dosage formulation comprising about 100 μg, 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg or 250 mg active ingredient.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

It will be appreciated that the amount of the NPY Y5 antagonist required for use in the treatment or prevention of major depressive disorders will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the patient's physician or pharmacist.

As used herein, the term "depression" includes major depressive episodes, major depressive disorder and seasonal affective disorder.

As used herein, the term "major depressive disorder" includes single or recurrent major depressive episodes, with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset and, in the case of recurrent episodes, with or without interepisode recovery and with or without seasonal pattern.

Other mood disorders encompassed within the term "major depressive disorder" include dysthymic disorder with early or late onset and with or without atypical features; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood.

Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

A "major depressive episode" is defined as at least two weeks of depressed mood or loss of interest, which may be accompanied by other symptoms of depression. The symptoms must persist for most of the day (i.e. for at least two thirds of the patients' waking hours), nearly every day (i.e. for at least ten out of fourteen days) for at least two consecutive weeks. A "depressed mood" is often described by the patient as feeling sad, hopeless, helpless or worthless. The patient may also appear sad to an observer, for example, through facial expression, posture, voice and

EXAMPLE 1

Y5 receptor antagonist assay:

To identify a potent Y5 antagonist for treatment of depression and /or anxiety in humans, the cloned human Y5 receptor is used in the primary assay. Vectors expressing either the 455 amino acid form (See, e.g., US 5,602,024) or a 10 amino acid, N-terminally shorter form (See, e.g., US 5,919,901) can be introduced into cell lines to obtain cells which express the human Y5 receptor. Binding of [^{125}I]PYY (NEN) to membrane preparations from cells expressing the cloned human Y5 receptor are performed in 0.2 ml of 25 mM Tris buffer (pH 7.4) containing 10 mM $MgCl_2$, 1 mM PMSF, 0.1% bacitracin and 0.5% bovine serum albumin. Membranes (10 - 300 μg/ml) prepared from LMtk-, COS-7, HEK or CHO cells expressing Y5 receptors, are incubated at 25°C for 120 min with [^{125}I]PYY (25 pM) in the presence of several concentrations of compounds to be evaluated. Bound and free peptides are separated by filtration using a GF/C glass filter presoaked with 0.3% polyethylenimine. The remaining radioactivity on the filter is quantitated using a TopCount™ (Packard Instruments Co. Inc.). Specific binding of [^{125}I]PYY is defined as the difference between total binding and nonspecific binding in the presence of 1 μM PYY. The binding IC_{50} is calculated using GraphPad Prism (Ver. 3.0).

The functional potency of Y5 antagonists can be determined using various assays which measure inhibition of second messenger pathways. NPY increases intracellular Ca^{2+} concentration via activation of Y5 receptors through coupling to Gαqi5. The potency of a Y5 antagonist in blocking NPY mediated Ca^{2+} increase can be used as a measure of its functional antagonist activity. For example, CHO cells expressing both NPY Y5 receptors and Gαqi5 are seeded (40,000 cells per well) into 96-well plate 24 hr before assay. Cells are loaded for 1 hr with a Ca^{2+}-sensitive fluorescent dye, Fluo-4-AM in assay buffer (Hank's Balanced Salts Solution (HBSS) containing 20 mM HEPES, 0.5 % BSA and 2.5 mM probenecid, pH 7.4), washed 3 times with the assay buffer, then returned to the incubator for 1 hr before assay on a fluorometric imaging plate reader, FLIPR™ (Molecular Device, California). The NPY-induced maximum change in fluorescence over baseline is determined and the dose which induces a 50% increase in fluorescence is defined as the EC_{50} dose for NPY. To evaluate Y5 antagonists, the assay is repeated with the EC_{50} dose of NPY in the presence of various concentrations of a Y5 antagonist to

tubing. The injector extended 2 mm beyond the end of the guide cannula. Bovine PP was dissolved in 10 mM PBS containing 0.05 % BSA. Two hour post-injection food intake was measured for each rat.

Results:

A Y5 antagonist was orally administered 1 hour prior to the ICV-injection of bPP in satiated male Sprague-Dawley rats. Effective compounds suppressed bPP-induced food intake in a dose-dependent manner, with a minimum effective dose between 3 and 50 mg/kg.

EXAMPLE 3

Separation-Induced Vocalization a rodent model of depression and anxiety

Male and female guinea-pigs pups are housed in family groups with their mothers and littermates throughout the study. Experiments are commenced after weaning when the pups are 2 weeks old. Before entering an experiment, the pups are screened to ensure that a vigorous vocalization response is reproducibly elicited following maternal separation. The pups are placed individually in an observation cage (55cm x 39cm x 19cm) in a room physically isolated from the home cage for 15 minutes and the duration of vocalization during this baseline period is recorded. Only animals which vocalize for longer than 5 minutes are employed for drug challenge studies (approximately 50% of available pups may fail to reach this criterion). On test days each pup receives an oral dose or an s.c. or i.p. injection of test compound or vehicle and is then immediately returned to the home cage with its mother and siblings for 30 to 60 minutes (or for up to 4 hours following an oral dose, dependent upon the oral pharmacokinetics of the test compound) before social isolation for 15 minutes as described above. The duration of vocalization on drug treatment days is expressed as a percentage of the pre-treatment baseline value for each animal. The same subjects are retested once weekly for up to 6 weeks. Between 6 and 8 animals receive each test compound at each dose tested.

CNS-penetrant NPY Y5 receptor antagonists of use in the present invention are also effective in the attenuation of separation-induced vocalizations by guinea-pig pups as hereinafter defined.

Essentially, a vocalization response in guinea-pig pups is induced by isolation from their mothers and littermates, which response is attenuated when a

WHAT IS CLAIMED IS:

1. A method for treating depression in a mammal which comprises administering to the mammal an effective amount of a NPY Y5 antagonist.

2. A method for treating anxiety in a mammal which comprises administering to the mammal an appropriate amount of a NPY Y5 antagonist.

3. A method for treating dementia in a mammal which comprises administering to the mammal an appropriate amount of a NPY Y5 antagonist.

4. The method of Claim 1 wherein the mammal is a human.

5. The method of Claim 1 wherein the NPY Y5 antagonist is an orally active NPY Y5 antagonist.

6. The method of Claim 1 wherein the NPY Y5 antagonist is a non-peptidal NPY Y5 antagonist.

7. The method of Claim 1 wherein the NPY Y5 antagonist is a CNS-penetrating NPY Y5 antagonist.

8. The method of Claim 2 wherein the mammal is a human.

9. The method of Claim 8 wherein the neuropeptide Y Y5 antagonist is a CNS-penetrating NPY Y5 antagonist.

10. The method of Claim 3 wherein the mammal is a human.

11. The method of Claim 10 wherein the neuropeptide Y Y5 antagonist is a CNS-penetrating NPY Y5 antagonist.

12. A method for preventing depression in a mammal comprising administration to said mammal an effective amount of a NPY Y5 antagonist, or a pharmaceutically acceptable salt or ester thereof.

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/US 02/40012

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/00 A61K31/438 A61K31/352 A61P25/22 A61P25/24 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 326 375 B1 (TAKAHASHI TOSHIYUKI ET AL) 4 December 2001 (2001-12-04) cited in the application column 30, line 49 -column 31, line 46; claim 1; table 1 column 64, line 31 - line 42	1-17
X	WO 00 27845 A (BANYU PHARMA CO LTD ;FUKURODA TAKAHIRO (JP); KANATANI AKIO (JP); F) 18 May 2000 (2000-05-18) cited in the application page 34, line 1 - line 9; claim 1; examples 19,20	1-17
X	EP 0 992 239 A (BANYU PHARMA CO LTD) 12 April 2000 (2000-04-12) cited in the application page 4, line 7 - line 39; claim 3	1-17

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2003	13/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Vandenbogaerde, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ional application No.
PCT/US 02/40012

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ation on patent family members

Interna Application No
PCT/US 02/40012

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 6326375 B1	04-12-2001	AU	6476200 A	19-03-2001
		BG	106390 A	29-12-2002
		BR	0013423 A	07-05-2002
		CN	1370168 T	18-09-2002
		CZ	20020533 A3	14-08-2002
		EP	1204663 A1	15-05-2002
		HU	0203107 A2	28-12-2002
		WO	0114376 A1	01-03-2001
		JP	2002030086 A	29-01-2002
		NO	20020814 A	15-04-2002
		SK	2522002 A3	06-08-2002
		TR	200200408 T2	21-06-2002
		US	2002188124 A1	12-12-2002
		US	6462053 B1	08-10-2002
		US	2002165391 A1	07-11-2002
		US	6335345 B1	01-01-2002
		US	2002052371 A1	02-05-2002
WO 0027845 A	18-05-2000	AU	1473200 A	29-05-2000
		EP	1129089 A1	05-09-2001
		JP	2002529464 T	10-09-2002
		WO	0027845 A1	18-05-2000
		US	6191160 B1	20-02-2001
		US	6313298 B1	06-11-2001
		US	2002058813 A1	16-05-2002
EP 0992239 A	12-04-2000	AU	7079498 A	13-11-1998
		EP	0992239 A1	12-04-2000
		US	6258837 B1	10-07-2001
		WO	9847505 A1	29-10-1998
WO 9720820 A	12-06-1997	AU	7626496 A	27-06-1997
		WO	9720820 A1	12-06-1997
		ZA	9610023 A	01-06-1997
WO 9910330 A	04-03-1999	AU	8914798 A	16-03-1999
		CA	2301821 A1	04-03-1999
		EP	1007514 A1	14-06-2000
		JP	2001514173 T	11-09-2001
		WO	9910330 A1	04-03-1999